

REMARKS

Applicants have amended claim 14 to clarify the invention and submitted new claim 21 for entry and consideration. Support for the amendment of claim 14 and for new claim 21 is found on page 18, line 28, on page 47, lines 24-28, and on page 48, lines 7-8 of the specification. No new matter is added by the amendment of claim 14 or by the submission of new claim 21.

Applicants respectfully request that, upon allowance of product claims, method claims 7-14 should be rejoined. The Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 USC § 103(b)" sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

Rejection under 35 USC § 101

The Examiner has rejected claims 2-14 under 35 USC § 101, based on the allegation that "the claimed invention is not supported by either a specific asserted utility or a well established utility". This rejection is traversed.

Applicants hereby submit DECLARATION UNDER 37 CFR 1.132 OF PREETI G. LAL. As shown in the Declaration and now well known in the art, the claimed polynucleotides encode HRM-19 which is a mitochondrial carrier protein. In the Declaration, Dr. Lal discusses the differential expression of mRNA encoding the polypeptide in lung cancer as demonstrated in the microarray data shown in Exhibit D. This specific utility was asserted at the time of filing and is described in the specification on page 47, line 28, and on page 48, lines 7-8. Thus, the Declaration presents evidence from an inventor who is also a person skilled in the art which ~~rebutts the rejection under 35 USC § 101.~~

The Examiner stated that "the specification does not assert any specific utility for HRM-19 and provides no additional evidence that HRM-19 has any specific function". (OA page 3, lines 8-10).

Applicants kindly point out that, as disclosed in the specification on page 18, lines 24-28, the amino acid sequence of HRM-19, i.e., SEQ ID NO:19 (which is encoded by the polynucleotide sequence of SEQ ID NO:68) shares homology with C. elegans Cl6C10 carrier protein and has a specific motif characteristic of a mitochondrial carrier protein. Further, as shown in DECLARATION UNDER 37 CFR 1.132 OF PREETI G. LAL, the amino acid sequence of HRM-19 belongs to the CGI-69 family of mitochondrial carrier proteins and is identical to human CGI-69 except for one amino acid change. As such, one of skill in the art would reasonably conclude that the claimed polynucleotides encode polypeptides which would more likely than not be mitochondrial carrier proteins. The fact that HRM-19 is nearly identical to another polypeptide known to be a mitochondrial carrier protein by itself demonstrates substantial utility, namely, the polypeptides that catalyze the exchange of substrates across the membrane (for example, see Palmieri, page 48).

The Examiner also stated that "it is nearly impossible from sequence homology alone to attribute a specific and substantial function for the protein" (OA, page 3, lines 12-13).

Applicants respectfully submit that evolutionary homology between two sequences without evidentiary support is in fact routinely used and readily accepted by one skilled in the art as a reliable predictor of function especially where the homologs belong to a family of proteins with conserved structure. In fact, at a recent Biotechnology Customer Partnership Meeting held at the USPTO on 17 April 2001, in a talk by Senior Examiner James Martinell, it was emphasized that when an Applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology", this can be an effective assertion of function for the claimed sequence. According to Dr. Martinell, after searching the prior art for the claimed protein, the question is "Would one of skill in the art accept that the protein has been placed in the correct family of proteins"? From handouts of Dr. Martinell's slides (emphasis added), the three possible answers can be deduced from the prior art search are:

- The search does not reveal any evidence that the family attribution made in the application is either incorrect or may be incorrect
- The protein either more likely belongs to a family other than that asserted in the application or likely does not belong to the family asserted in the application
- The search shows that the attribution is likely correct

In this Office Action, the Examiner has not cited evidence that claimed protein is not characterized as to its proper family. Indeed, based on the findings of Dr. Lal, the functional characterization of HRM-19 as a mitochondrial carrier protein by motif in the specification is validated in the Yu article attached to the Declaration. It is completely clear that HRM-19 belongs to the CGI-69 family of mitochondrial carrier proteins.

The Examiner also stated, "Such data would include the number of the specific domains associated with said function, and location of highly conserved charge-pairs" (OA at page 3, lines 14-16).

Applicants disclosed in the specification on page 18, lines 26-27, that the amino acid sequence of HRM-19, has a specific motif characteristic of a mitochondrial carrier protein. Furthermore, as shown in DECLARATION UNDER 37 CFR 1.132 OF PREETI G. LAL, the HRM-19 protein structure which is consistent with CGI-69 indicates the presence of four mitochondrial carrier domains, six potential transmembrane spanning regions, a likely mitochondrial localization and three regions with reasonable homology to putative mitochondrial energy-transfer signature motifs present in known uncoupling protein functional family members. Therefore, the Declaration and these attached references provide evidentiary support that one skilled in the art would more likely than not concur with Applicant's asserted functional characterization of the HRM-19 as a mitochondrial carrier protein.

The Examiner further stated that "one of ordinary skill in the art would not know which compound is a substrate for the carrier" (OA at page 3, lines 17-18, and cited pages 48-49 of the Palmeiri reference).

Applicants respectfully argue that the differential expression of the protein or the polynucleotide encoding it in lung cancer is a specific, real world utility and knowing the substrate for the protein would not provide any additional information relative to this utility.

The Examiner yet further stated that, "for a method of detection of a nucleic acid in a sample to be useful, one must know the biological significance of the polypeptide which is being detected" (OA at page 4, lines 5-7).

Applicants respectfully submit that knowledge of the biological function or role of a molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the USPTO acknowledged as much (66 FR at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, e.g., it hybridizes near a disease-associated gene or it has gene-regulating activity.

Applicants kindly thank the Examiner for pointing out that Kobayashi *et al.* show a real world utility for a mitochondrial protein in type II citrullinaemia; but as stated above, the differential expression of either the polypeptide or polynucleotide in lung cancer confers a far greater, real world benefit. Applicants further submit that the application is enabled (see EXAMPLE VII, page 57 of the specification) so that one skilled in the art would know how to use the polynucleotide or polypeptide with lung samples to detect differential expression and diagnosis of lung cancer.

The Examiner still yet further stated that, "One needs to know, e.g. that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in a specific diseased tissue compared to normal tissue (overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease" (OA, page 5, lines 15-17).

Applicants respectfully point to the information supplied in the DECLARATION UNDER 37 CFR 1.132 OF PREETI G. LAI, which clearly demonstrates that the transcripts for HRM-19 were significantly, differentially, up-regulated (overexpressed) in lung tissue samples from cancer patients as compared to matched normal samples from the same patient. Therefore, HRM-19, and the cDNA encoding it, are of diagnostic use in detecting lung cancers.

By virtue of this Declaration, Applicants have more than exceeded the "practically useful", and "specific benefit" to the public standards for 35 USC § 101 utility as described in *Anderson v. Natta*, (480 F2d 1392, 1397, 178 USPQ 458; CCPA 1973) and *Brenner v. Manson* (383 US 519, 534-35, 148

USPQ 689; 1966). Clearly, an invention that can be used to diagnose lung cancer is both practically useful and confers a specific benefit to the public. Applicants respectfully point out that the threshold for demonstration of utility is "not statistical certainty" as promulgated by the court in *Nelson v. Bowler* (626 F.2d 853, 856-57, 206 USPQ 881, 883-84). Furthermore, and in contrast to criminal cases, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt" (*In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354; CCPA 1965; MPEP 2107.02, section VII; CCPA 1980).

Applicants respectfully submit by virtue of the disclosure in the specification as filed and with the Declaration of Dr. Lal who is clearly a person skilled in the art, that the claimed invention is more than capable of providing an identifiable benefit--the detection of differential expression of the claimed polypeptide or polynucleotide in lung tissue for the diagnosis of lung cancer. And certainly, the claimed invention beyond its known association with type II citrullinaemia is useful in achieving a diagnostic result.

The Examiner has pointed out that claims 13 and 14 are drawn to a method of diagnosing an unspecified disease--cancer or immune response. Applicants have amended claim 14 to recite, "The method of claim 13 wherein expression is diagnostic of lung cancer", thereby specifying the particular disease for which the molecules are most useful.

The Examiner also stated that, "it appears that the main utility of the polypeptide and nucleic acid is to carry out further research to identify the biological function and possible diseases associated with said function. Substantial utility defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utility" (OA at page 6, lines 24-26).

Based on the arguments presented above, the teachings in the specification, and the DECLARATION UNDER 37 CFR 1.132 OF PREETI G. LAL, Applicants submit that no additional research is required in order to use the claimed polypeptide or polynucleotides as diagnostics for lung cancer.

Applicants agree with the Examiner that, in addition to conferring a specific benefit on the public, the benefit must also be "substantial". The real world utility discussed above is quite substantial. Applicants believe that once they have identified a specific utility, the claimed invention is presumed to possess it. (*In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed Cir 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed Cir 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. To do so, the Patent Office must provide evidence or sound scientific reasoning. See *In re Langer* (503 F.2d 1380, 1391-92, 183 USPQ 288; CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal

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evidence that would convince the person of ordinary skill that there is sufficient proof of utility (Branan, 51 F.3d at 1566). The applicant need only prove a "substantial likelihood" of utility; certainty is not required (Brenner, 383 US at 532).

With the DECLARATION UNDER 37 CFR 1.132 OF PREETI G. LAL, the EXHIBITS, arguments, and explanations above, Applicants respectfully request that the rejection of claims 2-14 under 35 USC § 101 be withdrawn.

Rejections under 35 USC § 112

The Examiner has rejected claims 2-14 under 35 USC § 112, first paragraph, based on the rejection of these claims for lack of utility under 35 USC § 101.

Applicants respectfully submit that they have provided sufficient evidence to clearly demonstrate that the 35 USC § 101 utility requirement has been satisfied. Therefore, Applicants respectfully request withdrawal of the rejection of claims 2-14 under 35 USC § 112, first paragraph.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is in condition for allowance, and early notice to that effect is earnestly solicited. If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, the Examiner is invited to contact the Applicants' Agent below at (650) 855-0555.

Respectfully submitted,
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"Version with Markings to Show Change Made"

IN THE CLAIMS

Please amend claim 14 as shown below:

14. (Once Amended) The method of claim 13 wherein expression is diagnostic of lung cancer [or immune response].

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